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Paraneoplastic Pemphigus: Recent Advances

Speaker: Dr. Grant J. Anhalt

The term paraneoplastic pemphigus (PNP) was first proposed by Dr. Anhalt in 1990. It was used to describe a previously unrecognized autoimmune mucocutaneous disease linked to underlying lymphoproliferative neoplasm. His original report consisted of only five cases. Since that time, the disease has been recognized throughout the world. More than 100 cases have now been reported.

These confirmatory reports have verified all the essential features of the disease that was first described. Mucosal ulceration in the form of intractable stomatitis is the most constant clinical feature of the disease. In no case to-date has this been absent. Cutaneous manifestations including blisters, lichenoid eruption or erythema multiforme like lesions are highly variable. These can change in an individual patient according to the stage of the disease. Histopathology also varies in line with the clinical picture: suprabasal acantholysis in blistering areas, vacuolar interface changes and individual keratinocyte necrosis in non-blistering areas.

Direct immunofluorescence usually shows intercellular and basement membrane zone deposits consisting of IgG and complements. This has a sensitivity of 80% and an accuracy of 80%. Circulating polyclonal IgG autoantibodies have been identified in patients with PNP. These were found to be acting against following antigens: desmoplakin I (250kd), BP antigen (230kd), Envoplakin/desmoplakin II (210kd), periplakin (190kd), desmoglein III (130kd) and a yet unidentified antigen (170kd). Immunoprecipitation is now used as definitive test, with a sensitivity greater than 90%.

The association of PNP with neoplasm was reviewed recently. Out of 126 reported cases, the frequency of association of various neoplasia with this syndrome is as follows: non-Hodgkin's lymphoma (46%), chronic lymphocytic leukaemia (18%), Castleman's tumour (16%), thymoma (9%), sarcoma (7%) and Waldstrom's macroglobulinaemia (4%). An interesting age distribution was noted among these cases. In patients with PNP associated with Castleman's disease, their age ranged from 20 to 30 years. In the rest, the age range was 50 to 70. Thus one should search hard for Castleman's disease in young patients under 30 years of age with PNP.

Prognosis of PNP depends on the nature of associated neoplasm. In 114 cases studied, 89 patients died, 14 patients were alive but with active disease, 11 patients were in remission. Poor prognostic factors included non-Hodgkin's lymphoma and respiratory involvement. The latter is usually a late complication. Bronchial biopsy will show acantholysis of bronchial epithelium. Patients with localized Castleman's disease and mainly lichenoid eruption had good prognosis.

Excision of associated benign tumour such as thymoma or localized Castleman's disease will result in either substantial improvement or complete remission of PNP. In patients with malignant neoplasia, there is yet no consensus regarding a therapeutic regimen that is consistently effective. The mainstay of treatment is with prednisolone at a dosage of 1-2mg/kg/day. In patients with chronic lymphocytic leukaemia, treatment worth trying includes cyclosporin A with or without cyclophosphamide. Overall mortality of PNP associated with malignant neoplasia is more than 90%.

Learning points:

Mucosal ulceration in the form of intractable stomatitis is the most constant clinical feature of paraneoplastic pemphigus.

Treatment of Severe Drug Eruptions

Speaker: Dr. J. C. Roujeau

Withdrawal of the suspected drug(s)

Dr. Roujeau and his colleagues have been frequently involved in the treatment of AIDS patients with drug eruptions. They studied the impact of the timing of drug withdrawal in a large retrospective series of patients with Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN). It was found that an earlier withdrawal of drugs with short elimination half-lives was associated with a better survival, while the withdrawal of drugs with long half-lives (>24h) did not improve the prognosis. It was therefore suggested that immediate withdrawal of suspected drug(s) should be a priority when dealing with a drug eruption.

Symptomatic treatment

In case of 'acute skin failure' (exfoliative dermatitis, TEN) management of patients must be undertaken in intensive care units or in burn units. The main principles of symptomatic therapy are the same as for major burns: warming of environment, correction of electrolyte disturbances, high caloric intake, and prevention of sepsis.

Specific therapy

The hypothesis of an immunologic basis for most drug eruptions provided a rationale for using corticosteroids, immunosuppressive drugs and anti-cytokines. Systemic corticosteroids are probably useful in 'hypersensitivity syndrome' when there is predominant lesional infiltration by activated eosinophils. Systemic corticosteroids were shown to be deleterious in cases of advanced TEN. Their potential usefulness at the very early stages of SJS or TEN remains controversial. High intravenous doses of cyclophosphamide have been administered to a few patients with TEN following an ineffective treatment with corticosteroids for 1 to 5 days. It remains doubtful that the progression of the lesions was shorter than expected. Cyclosporin A has also been used in a few patients with a claimed benefit on the progression of the disease. In 2 out of 4 cases, the disease recurred. This unusual event might suggest a rebound phenomenon. A few patients appeared to benefit from treatment with pentoxifyllin, owing to its suppressive effect on the production of tumour necrosis factor (TNF). Thalidomide, another suppressor of TNF

production, increased significantly the death rate when tested in a double-blind placebo controlled trial in patients with early TEN.

Measures to avoid recurrences

Patient and their first degree relatives should be given a written advice to avoid use of the responsible drug and chemically related compounds. Cases should be notified to regulatory agencies.

Learning points:

In severe drug eruptions, an earlier withdrawal of suspected drugs with short elimination half-lives was associated with a better survival.

Analysis of the T Cells Involved in Autoantibody Production in Pemphigus Vulgaris

Speaker: Dr. Michael Hertl

Pemphigus vulgaris (PV) is the classical example of an autoimmune disease of the skin. Its pathogenesis is mediated by circulating autoantibodies against distinct inter-keratinocyte antigen of human epidermis. It has been shown that IgG from PV sera reactive with desmoglein 3 (Dsg3), a desmosomal adhesion molecule, induced a disease resembling PV upon transfer into newborn mice. There is also evidence that autoreactive T-cells are present in antibody-mediated autoimmune diseases, such as myasthenis gravis and autoimmune thyroiditis. Involvement of CD4+ T lymphocytes in the pathogenesis of PV has been further suggested by the strong association of PV with the HLA class II alleles HLA-DR14. Recognition of epitopes of Dsg3, the autoantigen of PV, may thus be crucial for the initiation and perpetuation of Dsg3-specific T-cell responses. This then provides help to the B cells that produce Dsg3-specific autoantibodies.

Dr. Hertl and colleagues therefore sought to identify autoreactive T cells in patients with PV. They identified autoreactive T cells recognizing distinct epitopes of the extracellular portion of Dsg3 in the peripheral blood of PV patients with active disease.

These T cells produced both Th1 and Th2 cytokines. While the Th2 cytokines IL-4 and IL-13 have been shown to regulate the secretion of IgG4 and IgE by activated B cells, the Th1 cytokine IFN- γ induces the secretion of IgG1. Both autoreactive Th1 and Th2 cells may be involved in the regulation of the production of pathogenic autoantibodies by B cells in PV. This is because sera of patients with PV contain Th1-regulated IgG1 and Th2-regulated IgG4 autoantibodies directed against Dsg3.

Moreover, healthy individuals who carry MHC alleles similar or identical to those found to be highly prevalent in PV patients may also develop T cell responses to Dsg3. Carriers of particular HLA class II alleles thus seem to be genetically at risk to develop Dsg3-specific T cell responses. In contrast to PV

patients, autoreactive T cells from healthy donors produced predominantly the Th1 cytokine IFN- γ , but no Th2 cytokines. These observations point out that Dsg3-specific Th2 cells are restricted to PV patients. It may thus provide primary target to specifically modulate the T cell-dependent production of pathogenic autoantibodies in PV.

Learning points:

Dsg3-specific autoreactive T cells mediate in the pathogenesis of PV through production of Th1 and Th2 cytokines which in turn stimulate B cells production of Dsg3-autoantibodies.